General

Guideline Title

Paget's disease of bone: an Endocrine Society clinical practice guideline.

Bibliographic Source(s)

Singer FR, Bone HG, Hosking DJ, Lyles KW, Murad MH, Reid IR, Siris ES, Endocrine Society. Paget's disease of bone: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Dec;99(12):4408-22. [98 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Diagnosis

Imaging

In patients with suspected Paget's disease, the Task Force recommends obtaining plain radiographs of the suspicious regions of the skeleton. (1|++++)

In patients diagnosed with Paget's disease, the Task Force suggests a radionuclide bone scan to determine the extent of the disease and identify possible asymptomatic sites. (2|+++O)

Biochemistry

The Task Force recommends that after radiological diagnosis of Paget's disease, the initial biochemical evaluation of a patient should be done using serum total alkaline phosphatase (ALP) or with the use of a more specific marker of bone formation when appropriate. (1|++++)

The Task Force recommends measuring a specific marker of bone formation or resorption in patients with Paget's disease and abnormal liver or biliary tract function to assess response to treatment or follow evolution of the disease in untreated patients. (1|+++O)

Treatment

Indications

The Task Force recommends treatment with a bisphosphonate (see Table 2 in the original guideline document) for most patients with active Paget's disease who are at risk of future complications. (1|+++O)

Choice of Medication

The Task Force suggests a single 5-mg dose of intravenous (IV) zoledronate as the treatment of choice in patients without contraindications. (2|+++O)

Assessing the Response to Treatment

If there is urgency in the control of symptoms or the disease is particularly active, the Task Force suggests the use of short-term response of bone resorption markers before and shortly after treatment to indicate that an adequate therapeutic response is likely. (2|++OO)

The Task Force suggests that patients who have osteolytic lesions of Paget's disease have a repeat x-ray approximately 1 year after radiological diagnosis to determine whether there has been improvement with therapy or worsening in the absence of therapy. Subsequent x-rays may be considered in the event of persistent elevations of biochemical markers of bone turnover or the presence of bone pain and to determine when there is resolution of the lesion. (2|++OO)

Maintaining Remission

The Task Force suggests that to maximize the duration of remission, bone turnover should be reduced below the midpoint of the reference range for the chosen monitoring bone turnover marker. (2|++OO)

Relapse and Retreatment

The Task Force recommends that in patients with increased bone turnover, biochemical follow-up should be used as a more objective indicator of relapse than symptoms. (1|+++O)

Monostotic Paget's Disease

The Task Force suggests that amino-terminal propeptide of type 1 collagen (P1NP) or bone-specific ALP (BSAP) and βC-terminal propeptide of type 1 collagen (βCTx) or N-terminal propeptide of type 1 collagen (NTx) should be used for assessing the activity of untreated monostotic Paget's disease, although these may be normal when evidence of disease activity is still clearly demonstrated on scintigraphy. (2|++OO)

Management of the Complications of Paget's Disease

Hearing Loss

The Task Force suggests treatment with a potent bisphosphonate to prevent worsening of a hearing deficit. (2|++OO)

Osteoarthritis

The Task Force suggests the use of analgesics as adjunctive therapy for mild-to-moderate joint pain due to joint cartilage deterioration in patients with Paget's disease adjacent to the painful joint. (2|++OO)

For patients with severe osteoarthritis adjacent to Paget's disease of bone, the Task Force suggests bisphosphonate therapy before undergoing elective total joint replacement to prevent intraoperative hemorrhaging and postoperative loosening of the prosthesis. (2|++OO)

Bowing of Lower Extremity

The Task Force suggests treatment with a potent bisphosphonate before elective surgery for patients who require an osteotomy to correct severe bowing of the lower extremity associated with impaired ambulation and/or severe joint pain. (2|++OO)

Paralysis

In cases of paraplegia associated with Paget's disease of the spine, the Task Force suggests immediate treatment with a potent IV bisphosphonate associated with neurosurgical consultation. Surgical intervention may not be necessary after effective medical treatment unless there is severe structural damage. (2|++OO)

Neoplasms

The Task Force suggests that patients with osteosarcoma or a giant cell tumor be evaluated by an orthopedic surgeon (ungraded recommendation). If surgery is planned, the Task Force suggests pretreatment with a potent bisphosphonate to reduce bleeding from adjacent pagetic bone. (2|++OO)

Congestive Heart Failure

The Task Force suggests treatment with a bisphosphonate in patients with Paget's disease and congestive heart failure. (2|++OO)

Definitions

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Paget's disease of the bone

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To formulate practice guidelines for the diagnosis and treatment of Paget's disease of the bone

Target Population

Patients with suspected or confirmed Paget's disease of the bone

Interventions and Practices Considered

Diagnosis

1. Imaging (plain radiographs and radionuclide bone scan)
2. Measurement of serum total alkaline phosphatase (ALP) or a more specific marker of bone formation or resorption

Treatment/Management

1. Bisphosphonate treatment (single 5-mg dose of intravenous (IV) zoledronate as treatment of choice)
2. Assessing response to treatment using bone resorption markers and repeat x-rays
3. Maintaining remission through reduction of bone turnover
4. Retreatment after relapse
5. Use of amino-terminal propeptide of type 1 collagen (P1NP) or bone-specific ALP (BSAP) and βC-terminal propeptide of type 1 collagen (βCTx) or N-terminal propeptide of type 1 collagen (NTx) for assessing the activity of untreated monostotic Paget's disease
6. Management of complications of Paget's disease
    - Hearing loss
    - Osteoarthritis
    - Bowing of lower extremity
    - Paralysis
    - Neoplasms
    - Congestive heart failure

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Correlation between bone turnover marker levels and scintigraphic activity at baseline and after bisphosphonate treatment
- Correlation between different bone turnover marker levels and sensitivity of bone turnover markers to detect disease activity
- Disease remission
- Quality of life
- Adverse effects of treatment
- Improvement in bone pain
- Reduction in cardiac output

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Endocrine Society's Task Force commissioned a systematic review and meta-analysis (see the "Availability of Companion Documents" field) to evaluate the utility of the available biomarkers in the care of patients with Paget's disease of the bone.

Inclusion and Exclusion Criteria

Eligible studies were any type of study that evaluated the utility of using bone turnover markers in patients diagnosed with Paget's disease. In this review, bone scintigraphy was considered as the gold standard to determine disease activity. The bone turnover markers of interests are total alkaline phosphatase (ALP), bone ALP, amino-terminal procollagen type 1 propeptide (P1NP), serum and urine C-terminal telopeptide (sCTx and uCTx) (alpha or beta isoforms), and urine N-terminal telopeptide (uNTx). Because reviewers were also aiming to evaluate the usefulness of these markers in assessing disease activity after treatment with bisphosphonates, studies that evaluated the utility of bone turnover markers in patients undergoing bisphosphonate treatment were included. Studies that did not report the outcome of interest (correlation coefficient factor between the markers and bone scintigraphy or sensitivity of bone turnover markers to detect Paget's disease) were excluded. Reviewers also excluded publications without original data (clinical reviews and editorials), as well as studies with no available full-text paper. No language or country restrictions were used.

Data Sources and Search Strategy

A comprehensive search of several databases from each database's earliest inception to October 2012, which was updated to include studies to December 2014, in any language, was conducted. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for serum and urinary biological markers of Paget's disease. The electronic search was supplemented with manual search and review of bibliographies of included studies. The actual strategy is detailed as Appendix 1 of the systematic review (see the "Availability of Companion Documents" field).

Study Selection

Pairs of reviewers independently assessed each abstract for eligibility. Disagreement yielded an automatic inclusion in the upper level of screening. Included studies were retrieved as full text and they were screened in duplicate. Disagreement at this level was resolved by consensus. Information (baseline characteristics and results) were extracted by reviewers independently in duplicate. The principle investigator resolved conflicts in the reviewers' data by referring to the full-text article.

Number of Source Documents

The search identified 637 abstracts of which 18 studies met all the inclusion criteria and are included in the systematic review (see Figure 1 in the systematic review [see the "Availability of Companion Documents" field] for a flow chart of the screening process).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Endocrine Society's Task Force commissioned a systematic review and meta-analysis (see the "Availability of Companion Documents" field) to evaluate the utility of the available biomarkers in the care of patients with Paget's disease of the bone.

Data Extraction

Reviewers independently extracted study details from the full-text articles using a predesigned online form. The following data were abstracted: study design, country, patient characteristics (number of patients in each arm, sex, and age), follow-up period, details about their Paget's disease (treatment, disease progression, and/or response to treatment definition and markers used).

Assessment of Study Quality

The quality of included observational studies was assessed using the Newcastle–Ottawa scale by determining outcome ascertainment, adjustment for confounders, and proportion of patients lost to follow-up as well as sample selection. Quality of the randomized controlled trials (RCT) was assessed using Cochrane's Collaboration's tool by determining the randomization method, blinding, allocation concealment, lost to follow–up, and source of funding.

Statistical Analysis

The main outcome of interest was the correlation between bone turnover marker levels and scintigraphic activity at baseline and after bisphosphonate treatment. The correlation coefficient value and the number of subjects included in the study analysis were extracted. The correlation coefficient values range from −1, +1. Reviewers considered the correlation to be weak if the correlation coefficient value was less than 0.3, moderate if the value ranged between 0.3 and 0.7, and strong if the correlation coefficient value was greater than 0.7.

Other outcomes of interest were the correlation between different bone turnover marker levels and sensitivity of bone turnover markers to detect disease activity. Correlation coefficients were pooled across studies using the random effects model. Statistical analysis was conducted using Comprehensive Meta-Analysis (CMA) software.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Participants

The guideline was developed by an Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer.

Evidence

This evidence-based guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.

Consensus Process

One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines. Two systematic reviews were conducted to summarize supporting evidence.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Cost Analysis

- The recommendation to use total alkaline phosphatase (ALP) to screen for the metabolic activity of Paget's disease recognizes the low cost and universal availability of this test in both primary and secondary care. These advantages should be weighed against the greater specificity but somewhat higher cost and possibly restricted availability of more specific bone formation markers.
- For most patients, measurement of total ALP or other baseline disease activity markers at 6 to 12 weeks, when bone turnover will have shown a substantial decline, is an acceptable and cost-effective option.
- Indications for medical intervention are based on cost-effectiveness and a balancing of potential benefits against potential adverse effects. In the case of intravenous (IV) zoledronate for Paget's disease, intervention is usually cheaper (as a result of savings in costs of follow-up investigations and clinical appointments), and results in improved quality of life.
- Now that it is possible to produce disease remission that can be sustained for more than 6 years in the great majority of patients, it becomes more cost-effective and more convenient to treat most patients with active disease who do not have contraindications to IV zoledronate, simply to reduce the costs and time involved in follow-up.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Bisphosphonate treatment may be effective in preventing or slowing the progress of hearing loss and osteoarthritis in joints adjacent to Paget's disease and may reverse paraplegia associated with spinal Paget's disease.

Potential Harms

- Zoledronate has a satisfactory safety profile, the most common adverse event being a flu-like illness, which occurs in about 25% of patient. Patients need to be warned of this possibility. The frequency and severity of these reactions is reduced by about one-half with acetaminophen or nonsteroidal anti-inflammatory drugs, which can be used prophylactically. Uveitis and other inflammatory changes in the eye can be a part of the acute phase response, occurring in approximately 1% of patients receiving zoledronate. This requires prompt attention from an ophthalmologist and resolves rapidly and completely with topical steroids. Zoledronate is potentially nephrotoxic, so it should not be administered if the glomerular filtration rate is <35 mL/min. Some physicians use lower doses and longer infusion times in patients with marginal renal function, but this has not been approved by regulatory agencies. Potent bisphosphonates can produce symptomatic hypocalcemia in the presence of marked vitamin D deficiency (25-hydroxyvitamin <D 25 nmol/L). In those at risk of vitamin D deficiency, supplementation before treatment is advisable. A single, large, oral dose of calciferol, 100,000 U, appears to be satisfactory.
- The comparatively high doses of oral bisphosphonates required for the control of Paget's disease are associated with significant upper gastrointestinal side effects.

Contraindications

Contraindications

Some patients have contraindications to the use of intravenous (IV) zoledronate, such as marked renal impairment.

Qualifying Statements

Qualifying Statements

- Clinical Practice Guidelines are developed to be of assistance to endocrinologists and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Singer FR, Bone HG, Hosking DJ, Lyles KW, Murad MH, Reid IR, Siris ES, Endocrine Society. Paget's disease of bone: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Dec;99(12):4408-22. [98 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Dec

Guideline Developer(s)

The Endocrine Society - Professional Association

Source(s) of Funding

Funding for this guideline was derived solely from The Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Guideline Committee

The Paget's Disease of the Bone Task Force

Composition of Group That Authored the Guideline

Task Force Members: Frederick R. Singer (*Chair*), Henry G. Bone, III, David J. Hosking, Kenneth W. Lyles, Mohammad Hassan Murad, Ian R. Reid, Ethel S. Siris

Financial Disclosures/Conflicts of Interest

The Endocrine Society maintains a rigorous conflict of interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the Clinical Guidelines Subcommittee (CGS) before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (e.g., stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through The Endocrine Society office.

Financial Disclosures of the Task Force

Frederick R. Singer, MD (chair)—Financial or Business/Organizational Interests: The Paget Foundation, Fibrous Dysplasia Foundation, American Bone Health; Significant Financial Interest or Leadership Position: none

Henry G. Bone, III, MD—Financial or Business/Organizational Interests: The Paget Foundation, Novartis, Merck, Amgen, NPS, Takeda, Tarsa; Significant Financial Interest or Leadership Position: none declared

David J. Hosking, MD—Financial or Business/Organizational Interests: Osteoporosis International, Amgen, Novartis; Significant Financial Interest or Leadership Position: none declared

Kenneth W. Lyles, MD—Financial or Business/Organizational Interests: Amgen, BisCardia, Inc., Faculty Connection, LLC, Kirin Pharmaceuticals, Novartis, UCB; Significant Financial Interest or Leadership Position: The Paget Foundation

M. Hassan Murad, MD*—Financial or Business/Organizational Interests: KER Unit of the Mayo Clinic; Significant Financial Interest or Leadership Position: none declared

Ian R. Reid, MD—Financial or Business/Organizational Interests: International Bone, Mineral Society, American Society of Bone and Mineral Research, Merck, Novartis, Amgen, Lilly, Sanofi; Significant Financial Interest or Leadership Position: none declared

Ethel S. Siris, MD—Financial or Business/Organizational Interests: National Osteoporosis Foundation, The Paget Foundation, International Osteoporosis Foundation; Significant Financial Interest or Leadership Position: Eli Lilly, Merck, Novartis, Pfizer

*Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

Guideline Endorser(s)

European Society of Endocrinology - Medical Specialty Society

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from The Endocrine Society Web site .

Print copies: Available from The Endocrine Society, 2055 L St, NW, Suite 600, Washington, DC 20036; Phone: 202-971-3636; Email: Societyservices@endo-society.org

Availability of Companion Documents

The following is available:

- Al Nofal AA, Altayar O, BenKhadra K, Qasim Agha OQ, Asi N, Nabhan M, Prokop LJ, Tebben P, Murad MH. Bone turnover markers in Paget's disease of the bone: a systematic review and meta-analysis. Osteoporos Int. 2015 Jul;26(7):1875-91. Electronic copies: Available to subscribers from the Osteoporosis International Journal Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 21, 2015. The information was verified by the guideline developer on September 14, 2015.

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